

We claim:

1. A composition including a polypeptide comprising an antibody-based antigen-binding domain of human composition with binding specificity for an antigen expressed on the surface of a human cell, wherein treating cells expressing said antigen with a multivalent polypeptide having two or more of said antigen-binding domains causes or leads to killing of said cells in a manner where neither cytotoxic entities nor immunological mechanisms are needed for said killing.
2. A composition including a polypeptide comprising an antibody-based antigen-binding domain which binds to human HLA-DR with a K_d of 1 μ M or less, wherein treating cells expressing HLA-DR with a multivalent polypeptide having two or more of said antigen-binding domains causes or leads to killing of said cells in a manner where neither cytotoxic entities nor immunological mechanisms are needed for said killing.
3. A composition including a multivalent polypeptide comprising a plurality of antibody-based antigen-binding domains of human composition which specifically bind to human HLA-DR, wherein treating cells expressing HLA-DR with said multivalent polypeptide causes or leads to killing of said cells in a manner where neither cytotoxic entities nor immunological mechanisms are needed for said killing, wherein said antigen-binding domains individually bind to human HLA-DR with a K_d of 1 μ M or less.
4. A composition including a multivalent polypeptide comprising a plurality of antibody-based antigen-binding domains of human composition which specifically bind to human HLA-DR, wherein treating cells expressing HLA-DR with said multivalent polypeptide causes or leads to killing of said cells in a manner where neither cytotoxic entities nor immunological mechanisms are needed for said cell killing, wherein said multivalent polypeptide has an EC_{50} of 100 nM or less for killing activated lymphoid cells.
5. A composition including a polypeptide comprising at least one antibody-based antigen-binding domain that binds to human HLA-DR with a K_d of 1 μ M or less, said antigen-binding domain being isolated by a method which includes isolation of VL and VH domains of human composition from a recombinant antibody library by ability to bind to at least one

epitope of human HLA-DR, wherein treating cells expressing HLA-DR with a multivalent polypeptide having two or more of said antigen binding domains causes or leads to killing of said cells in a manner where neither cytotoxic entities nor immunological mechanisms are needed for said killing.

6. The composition of claim 5, wherein the method for isolating the antigen-binding domain includes the further steps of:
 - a. generating a library of variants of at least one of the CDR1, CDR2 and CDR3 sequences of one or both of the VL and VH domains, and
 - b. isolation of VL and VH domains from the library of variants by ability to bind to human HLA-DR with a K_d of 1 μ M or less.
7. The composition of any of claims 1-6, wherein the multivalent polypeptide has an EC_{50} for killing transformed cells at least 5-fold lower than the EC_{50} for killing normal cells.
8. The composition of any of claims 1-6, wherein the multivalent polypeptide has an EC_{50} for killing activated cells at least 5-fold lower than the EC_{50} for killing unactivated cells.
9. The composition of any of claims 1-6, wherein the multivalent polypeptide has an EC_{50} of 50 nM or less for killing transformed cells.
10. The composition of any of claims 1-6, wherein the multivalent polypeptide has an EC_{50} for killing lymphoid tumor cells of 10 nM or less.
11. The composition of any of claim 1-6, wherein the multivalent polypeptide kills activated lymphoid cells.
12. The composition of claim 11, wherein said activated lymphoid cells are lymphoid tumor cells representing a disease selected from the group consisting of B cell non-Hodgkin lymphoma, B cell lymphoma, B cell acute lymphoid leukemia, Burkitt lymphoma, Hodgkin lymphoma, hairy cell leukemia, acute myeloid leukemia, T cell lymphoma, T cell non-Hodgkin lymphoma, chronic myeloid leukemia, chronic lymphoid leukemia, and multiple myeloid leukemia.

21. The composition of claim 20, wherein said antigen-binding domain binds to at least 5 different of said HLA-DR types.
22. The composition of any one of claims 1-6, wherein said antigen-binding domain includes a combination of a VH domain and a VL domain, wherein said combination is found in one of the clones selected from the group consisting of MS-GPC-1, MS-GPC-6, MS-GPC-8, MS-GPC-10, MS-GPC-8-1, MS-GPC-8-6, MS-GPC-8-9, MS-GPC-8-10, MS-GPC-8-17, MS-GPC-8-18, MS-GPC-8-27, MS-GPC-8-6-2, MS-GPC-8-6-19, MS-GPC-8-6-27, MS-GPC-8-6-45, MS-GPC-8-6-13, MS-GPC-8-6-47, MS-GPC-8-10-57, MS-GPC-8-27-7, MS-GPC-8-27-10 and MS-GPC-8-27-41.
23. The composition of any one of claims 1-6, wherein said antigen-binding domain includes of a combination of HuCAL VH2 and HuCAL Vλ1, wherein the VH CDR3, VL CDR1 And VL CDR3 is found in one of the clones selected from the group consisting of MS-GPC-1, MS-GPC-8, MS-GPC-10, MS-GPC-8-1, MS-GPC-8-6, MS-GPC-8-9, MS-GPC-8-10, MS-GPC-8-17, MS-GPC-8-18, MS-GPC-8-27, MS-GPC-8-6-2, MS-GPC-8-6-19, MS-GPC-8-6-27, MS-GPC-8-6-45, MS-GPC-8-6-13, MS-GPC-8-6-47, MS-GPC-8-10-57, MS-GPC-8-27-7, MS-GPC-8-27-10 and MS-GPC-8-27-41.
24. The composition of any one of claims 1-6, wherein said antigen-binding domain includes a combination of HuCAL VH2 and HuCAL Vλ1, wherein the VH CDR3 sequence is taken from the consensus CDR3 sequence

XXXXRGXFDX (SEQ ID No. 1)

wherein each X independently represents any amino acid residue; and/or

wherein the VL CDR3 sequence is taken from the consensus CDR3 sequence

QSYDXXXX (SEQ ID No. 2)

wherein each X independently represents any amino acid residue.

25. The composition of claim 24, wherein the VH CDR3 sequence is SPRYGAFDY (SEQ ID No. 3) and/or the VL CDR3 sequence is QSYDLIRH (SEQ ID No. 4) or QSYDMNVH (SEQ ID No. 5).

26. The composition of any one of claims 1-6, wherein said antigen-binding domain competes for antigen binding with an antibody including a combination of HuCAL VH2 and HuCAL Vλ1, wherein the VH CDR3 sequence is taken from the consensus CDR3 sequence

XXXXRGXFDX (SEQ ID No. 1)

each X independently represents any amino acid residue; and/or

the VL CDR3 sequence is taken from the consensus CDR3 sequence

QSYDXXXX (SEQ ID No. 2)

each X independently represents any amino acid residue.

27. The composition of claim 26, wherein the VH CDR3 sequence is SPRYGAFDY (SEQ ID No. 3) and/or the VL CDR3 sequence is QSYDLIRH (SEQ ID No. 4) or QSYDMNVH (SEQ ID No. 5).

28. The composition of any one of claims 1-6, wherein said antigen-binding domain includes a VL CDR1 sequence represented in the general formula

SGSXXNIGXNYVX (SEQ ID No. 6)

wherein each X independently represents any amino acid residue.

29. The composition of claim 28, wherein the CDR1 sequence is SGSESNIGNNYVQ (SEQ ID No. 7).

30. The composition of any of claims 1-6, wherein the mechanism of said killing involves an innate pre-programmed process of said cell.

31. The composition of claim 30, wherein said killing is non-apoptotic.

32. The composition of claim 30, wherein said killing is dependent on the action of non-caspase proteases, and/or wherein said killing cannot be inhibited by zVAD-fmk or zDEVD-fmk.

33. The composition of any one of claims 1-6, wherein said antibody-based antigen-binding domain is part of a multivalent polypeptide including at least a F(ab')₂ antibody fragment or a mini-antibody fragment.

34. The composition of any one of claims 1-6, wherein said antibody-based antigen-binding domain is part of a multivalent polypeptide comprising at least two monovalent antibody fragments selected from Fv, scFv, dsFv and Fab fragments, and further comprises a cross-linking moiety or moieties.
35. The composition of any one of claims 1-6, wherein said antibody-based antigen-binding domain is part of a multivalent polypeptide comprising at least one full antibody selected from the antibodies of classes IgG₁, 2a, 2b, 3, 4, IgA, and IgM.
36. The composition of any one of claims 1-6, wherein said antibody-based antigen-binding domain is part of a multivalent polypeptide that is formed prior to binding to a cell.
37. The composition of any one of claims 1-6, wherein said antibody-based antigen-binding domain is part of a multivalent polypeptide that is formed after binding to a cell.
38. The composition of claim 3 or 4, wherein the antigen binding sites are cross-linked to a polymer.
39. A nucleic acid comprising a protein coding sequence for an antigen-binding domain comprised in any of claims 1-6, or a multivalent polypeptide thereof.
40. A vector comprising the nucleic acid of claim 39, and a transcriptional regulatory sequence operably linked thereto.
41. A host cell harboring a nucleic acid of claim 39.
42. A method for the production of composition comprising a multivalent polypeptide that causes or leads to killing of cells in a manner where neither cytotoxic entities nor immunological mechanisms are needed for said killing, comprising culturing the cells of claim 41 under conditions wherein the nucleic acid is expressed either as a multivalent polypeptide or as a polypeptide comprising at least one antigen binding domains which is subsequently treated to form a multivalent polypeptide composition.
43. The composition of any of claims 1-6, formulated in a pharmaceutically acceptable carrier and/or diluent.

44. The use of a composition of any of claims 1-6, for preparing a pharmaceutical preparation for the treatment of animals.
45. The use of a nucleic acid of claim 39 for preparing a pharmaceutical preparation for the treatment of animals.
46. The use of a host cell of claim 41 for preparing a pharmaceutical preparation for the treatment of animals.
47. The use of the method of claim 42 for preparing a pharmaceutical preparation for the treatment of animals.
48. The use according to claim 44, wherein said animal is a human.
49. The use according to claim 44, for the treatment of cell proliferative disorders, wherein said antibody-based antigen binding domain is part of a multivalent polypeptide.
50. The use according to claim 49, wherein said treatment is the treatment of disorders involving transformed cells expressing MHC class II antigens.
51. The use according claim 49, wherein said treatment is the treatment of a disorder selected from B cell non-Hodgkin lymphoma, B cell lymphoma, B cell acute lymphoid leukemia, Burkitt lymphoma, Hodgkin lymphoma, hairy cell leukemia, acute myeloid leukemia, T cell lymphoma, T cell non-Hodgkin lymphoma, chronic myeloid leukemia, chronic lymphoid leukemia, or multiple myeloid leukemia.
52. The use according to claim 44, wherein said treatment is the treatment of disorders involving unwanted activation of cells of the immune system, such as lymphoid cells expressing MHC class II.
53. The use according to claim 44, wherein said treatment is the treatment of a disorder selected from rheumatoid arthritis, juvenile arthritis, multiple sclerosis, Grave's disease, insulin-dependent diabetes, narcolepsy, psoriasis, systemic lupus erythematosus, ankylosing spondylitis, transplant rejection, graft vs. host disease, Hashimoto's disease, myasthenia

gravis, pemphigus vulgaris, glomerulonephritis, thyroiditis, pancreatitis, insulinitis, primary biliary cirrhosis, irritable bowel disease or Sjogren syndrome.

54. The use according to claim 44, wherein said disorder is selected from myasthenia gravis, rheumatoid arthritis, multiple sclerosis, transplant rejection or graft vs. host disease.
55. A diagnostic composition including the composition of any of claims 1-6.
56. The diagnostic composition of claim 55, further comprising a cross-linking moiety or moieties.
57. A method for killing a cell expressing an antigen on the surface of said cell comprising the step of treating the cell with a plurality of antigen-binding domains of any one of claims 1-6, wherein said antibody-based antigen-binding domains are part of a multivalent polypeptide, and where neither cytotoxic entities nor immunological mechanisms are needed to cause or lead to said killing.
58. A method to identify patients that can be treated with a composition of any of claims 1-6, formulated in a pharmaceutically acceptable carrier and/or diluent comprising:
- isolating cells from a patient;
 - contacting said cells with the composition of any of claims 1-6; and,
 - measuring the degree of killing or immunosuppression of said cells.
59. A kit to identify patients that can be treated with a composition of any of claims 1-6, formulated in a pharmaceutically acceptable carrier and/or diluent comprising:
- a composition of any of claims 1-6; and
 - means to measure the degree of killing or immunosuppression of said cells.
60. A kit comprising:
- a composition according to any one of claims 1-6, and

b. a cross-linking moiety.

61. A kit comprising:

a. a composition according to any one of claims 1-6, and

b. a detectable moiety or moieties, and

c. reagents and/or solutions to effect and/or detect binding of (a) to an antigen.

62. A cytotoxic composition comprising a composition of any one of claims 1-6 operably linked to a cytotoxic agent.

63. An immunogenic composition comprising a composition of any one of claims 1-6 operably linked to an immunogenic agent.

64. A method to kill a cell comprising contacting said cell with a composition of any one of claims 1-6 operably linked a cytotoxic or immunogenic agent.

65. The use of a composition of any one of claims 1-6 operable linked a cytotoxic or immunogenic agent for preparing a pharmaceutical preparation for the treatment of animals.

66. A composition including a polypeptide comprising at least one antibody-based antigen-binding domain with a binding specificity for a human MHC class II antigen with a K_d of 1 μ M or less, wherein treating cells expressing said antigen with said polypeptide causes or leads to suppression of an immune response.

67. A composition including a polypeptide comprising at least one antibody-based antigen-binding domain with a binding specificity for human HLA-DR antigen, wherein treating cells expressing HLA-DR with said polypeptide causes or leads to suppression of an immune response, and wherein said antigen-binding domain includes a combination of a VH domain and a VL domain, wherein said combination is found in one of the clones taken from the group consisting of MS-GPC-1, MS-GPC-6, MS-GPC-8, MS-GPC-10, MS-GPC-8-1, MS-GPC-8-6, MS-GPC-8-9, MS-GPC-8-10, MS-GPC-8-17, MS-GPC-8-18, MS-GPC-8-27, MS-GPC-8-6-2, MS-GPC-8-6-19, MS-GPC-8-6-27, MS-GPC-8-6-45, MS-GPC-8-6-13,

MS-GPC-8-6-47, MS-GPC-8-10-57, MS-GPC-8-27-7, MS-GPC-8-27-10 and MS-GPC-8-27-41.

68. A composition including a polypeptide comprising at least one antibody-based antigen-binding domain with a binding specificity for a human MHC class II antigen with a K_d of 1 μ M or less, said antigen-binding domain being isolated by a method which includes isolation of VL and VH domains of human composition from a recombinant antibody library by ability to bind to human MHC class II antigen, wherein treating cells expressing MHC Class II with said polypeptide causes or leads to suppression of an immune response.
69. The composition of claim 68, wherein the method for isolating the antigen-binding domain includes the further steps of:
- generating a library of variants at least one of the CDR1, CDR2 and CDR3 sequences of one or both of the VL and VH domains, and
 - isolation of VL and VH domains from the library of variants by ability to bind to human MHC class II antigen with a K_d of 1 μ M or less;
 - (optionally) repeating steps (a) and (b) with at least one other of the CDR1, CDR2 and CDR3 sequences.
70. The composition of any of claims 67, 68 or 69, wherein said antigen-binding domain binds to HLA-DR.
71. The composition of any of claims 66-69 wherein said antigen-binding domain binds to the β -chain of HLA-DR.
72. The composition of claim 71, wherein said antigen-binding domain binds to an epitope of the first domain of the β -chain of HLA-DR.
73. The composition of any of claims 66-69, wherein said cells are lymphoids cells.

27, MS-GPC-8-6-45, MS-GPC-8-6-13, MS-GPC-8-6-47, MS-GPC-8-10-57, MS-GPC-8-27-7, MS-GPC-8-27-10 and MS-GPC-8-27-41.

82. The composition of any of claims 66-69, wherein said antigen-binding domain includes a combination of HuCAL VH2 and HuCAL Vλ1, wherein the VH CDR3 sequence is taken from the consensus CDR3 sequence

XXXXRGXFDX (SEQ ID No. 1)

wherein each X independently represents any amino acid residue; and/or

wherein the VL CDR3 sequence is taken from the consensus CDR3 sequence

QSYDXXXX (SEQ ID No. 2)

wherein each X independently represents any amino acid residue.

83. The composition of claim 82, wherein the VH CDR3 sequence is SPRYGAFDY (SEQ ID No. 3) and/or the VL CDR3 sequence is QSYDLIRH (SEQ ID No. 4) or QSYDMNVH (SEQ ID No. 5).

84. The composition of any of claims 66-69, wherein said antigen-binding domain competes for antigen binding with an antibody including a combination of HuCAL VH2 and HuCAL Vλ1, wherein the VH CDR3 sequence is taken from the consensus CDR3 sequence

XXXXRGXFDX (SEQ ID No. 1)

each X independently represents any amino acid residue; and/or

the VL CDR3 sequence is taken from the consensus CDR3 sequence

QSYDXXXX (SEQ ID No. 2)

each X independently represents any amino acid residue.

85. The composition of claim 84, wherein the VH CDR3 sequence is SPRYGAFDY (SEQ ID No. 3) and/or the VL CDR3 sequence is QSYDLIRH (SEQ ID No. 4) or QSYDMNVH (SEQ ID No. 5).

86. The composition of any of claims 66-69, wherein said antigen-binding domain includes a VL CDR1 sequence represented in the general formula

SGSXXNIGXNYVX (SEQ ID No. 6)

wherein each X independently represents any amino acid residue.

87. The composition of claim 86, wherein the CDR1 sequence is SGSESNIGNNYVQ (SEQ ID No. 7).
88. The composition of any one of claims 66-69, wherein said suppression of an immune response is brought about by or manifests itself in down-regulation of expression of said antigen expressed on the surface of said cell.
89. The composition of any one of claims 66-69, wherein said suppression of an immune response is brought about by or manifests itself in inhibition of the interaction between said cell and other cells, wherein said interaction would normally lead to an immune response.
90. The composition of any one of claims 66-69, wherein said suppression of the immune response is brought about by or manifests itself in the killing of said cells.
91. The composition of claim 90, wherein said killing is mediated by binding of a plurality of antigen-binding domains, wherein said antibody-based antigen-binding domains are part of a multivalent polypeptide, and where neither cytotoxic entities nor immunological mechanisms are needed to causes or leads to said killing.
92. The composition of any one of claims 66-69, formulated in a pharmaceutically acceptable carrier and/or diluent.
93. A pharmaceutical preparation comprising the composition of claim 75 in an amount sufficient to suppress an immune response in an animal.
94. A pharmaceutical preparation comprising the composition of claim 76 in an amount sufficient to inhibit IL-2 secretion in an animal.

95. A pharmaceutical preparation comprising the composition of claim 77 in an amount sufficient to inhibit T cell proliferation in an animal.
96. The use of a composition of any one of claims 66-69, for preparing a pharmaceutical preparation for the treatment of animals, such as where said animals are human.
97. A nucleic acid including a protein coding sequence for a polypeptide of the composition of any of claims 66-69.
98. A vector comprising the coding sequence of claim 97, and a transcriptional regulatory sequence operably linked thereto.
99. A host cell harboring a nucleic acid selected from the group consisting of: a nucleic acid of claim 97 or the vector of claim 98.
100. A method for the production of an immunosuppressive composition, comprising culturing the cells of claim 99 under conditions wherein the nucleic acid is expressed.
101. A method for suppressing activation of a cell of the immune system, comprising treating the cell with a composition of any of claims 66-69.
102. A method for suppressing proliferation of a cell of the immune system, comprising treating the cell with a composition of any of claims 66-69.
103. A method for suppressing IL-2 secretion by a cell of the immune system, comprising treating the cell with a composition of any of claims 66-69.
104. A method for immunosuppressing a patient, comprising administering to the patient an effective amount of a composition of any of claims 66-69 to reduce the level of immunological responsiveness in the patient.
105. A method for killing a cell expressing an antigen on the surface of said cell comprising the step of treating the cell with a plurality of antigen-binding domains of any one of claims 66-69, wherein said antibody-based antigen-binding domains are part of a multivalent

polypeptide, and where neither cytotoxic entities nor immunological mechanisms are needed to causes or leads to said killing, such where said antigen is HLA-DR.

106. The use according to claim 96, wherein said treatment is the treatment of a disorder selected from rheumatoid arthritis, juvenile arthritis, multiple sclerosis, Grave's disease, insulin-dependent diabetes, narcolepsy, psoriasis, systemic lupus erythematosus, ankylosing spondylitis, transplant rejection, graft vs. host disease, Hashimoto's disease, myasthenia gravis, pemphigus vulgaris, glomerulonephritis, thyroiditis, pancreatitis, insulitis, primary biliary cirrhosis, irritable bowel disease or Sjogren syndrome.
107. The use according to claim 96, wherein said treatment is the treatment of a disorder selected from myasthenia gravis, rheumatoid arthritis, multiple sclerosis, transplant rejection or graft vs. host disease.
108. A method of suppressing the interaction of a cell of the immune system with an other cell, comprising contacting the cell with the composition of any of claims 66-69.
109. A method for conducting a pharmaceutical business comprising:
 - a. isolating one or more antigen-binding domains that bind to antigens expressed on the surface of human cells;
 - b. generating a multivalent composition, such as multivalent polypeptide, comprising a plurality of said antigen-binding domains, which multivalent composition kills with an EC_{50} of 50nM or less transformed or activated cells that express said antigen, where neither cytotoxic entities nor immunological mechanisms are needed to cause or lead to said killing;
 - c. conducting therapeutic profiling of the multivalent composition, for efficacy and toxicity in animals;
 - d. preparing a package insert describing the multivalent composition for treatment of proliferative disorders; and,
 - e. marketing the multivalent composition for treatment of proliferative disorders.

110. A method for conducting a life science business comprising:

- a. isolating one or more antigen-binding domains that bind to antigens expressed on the surface of human cells;
- b. generating a multivalent composition, such as multivalent polypeptide, comprising a plurality of said antigen-binding domains, which multivalent composition kills with an EC_{50} of 50 nM or less transformed or activated cells expressing said antigen where neither cytotoxic entities nor immunological mechanisms are needed to cause or lead to said killing;
- c. licensing, jointly developing or selling, to a third party, the rights for selling the multivalent composition.

111. The method of any of claims 109 or 110, wherein the antigen-binding domain is isolated by a method which includes:

- a. isolation of VL and VH domains of human composition from a recombinant antibody library by ability to bind to HLA-DR,
- b. generating a library of variants at least one of the CDR1, CDR2 and CDR3 sequences of one or both of the VL and VH domains, and ,
- c. isolation of VL and VH domains from the library of variants by ability bind to HLA-DR with a K_d of 1 μ M or less.

112. A method for conducting a pharmaceutical business comprising:

- a. isolating one or more antigen-binding domains that bind to MHC class II expressed on the surface of human cells with a K_d of 1 μ M or less;
- b. generating a composition comprising said antigen-binding domains, which composition is immunosuppressant with an IC_{50} of 100 nM or less;
- c. conducting therapeutic profiling of the composition for efficacy and toxicity in animals;

- d. preparing a package insert describing the use of the composition for immunosuppression therapy; and,
- e. marketing the composition for use as an immunosuppressant.

113. A method for conducting a life science business comprising:

- a. isolating one or more antigen-binding domains that bind to MHC class II expressed on the surface of human cells with a K_d of 1 μ M or less;
- b. generating a composition comprising said antigen-binding domains, which composition is immunosuppressant with an IC_{50} of 100 nM or less;
- c. licensing, jointly developing or selling, to a third party, the rights for selling the composition.

114. The method of any of claims 112 or 113, wherein the antigen-binding domain is isolated by a method which includes:

- a. isolation of VL and VH domains of human composition from a recombinant antibody library by ability to bind to HLA-DR,
- b. generating a library of variants at least one of the CDR1, CDR2 and CDR3 sequences of one or both of the VL and VH domains, and,
- c. isolation of VL and VH domains from the library of variants by ability to bind to HLA-DR with a K_d of 1 μ M or less.

115. The method of any of claims 109, 110, 112, and 113, wherein said antigen-binding domain comprises a combination of VH and VL domains found in the clones selected from the group consisting of MS-GPC-1, MS-GPC-8, MS-GPC-10, MS-GPC-8-1, MS-GPC-8-6, MS-GPC-8-9, MS-GPC-8-10, MS-GPC-8-17, MS-GPC-8-18, MS-GPC-8-27, MS-GPC-8-6-2, MS-GPC-8-6-19, MS-GPC-8-6-27, MS-GPC-8-6-45, MS-GPC-8-6-13, MS-GPC-8-6-47, MS-GPC-8-10-57, MS-GPC-8-27-7, MS-GPC-8-27-10 and MS-GPC-8-27-41.

116. A host cell harboring a vector of claim 40.